REMARKS/ARGUMENTS

Status of the Claims

Claims 35-52 have been rejected. Claims 35, 36, 38, 39, 41, 43, and 48 have been amended as noted below. No new matter has been added by way of claim amendment.

Claim 35 has been amended to recite "a single unit dose" of a therapeutically effective amount of a recombinant FGF-2. Accordingly, claims 36, 38, 39, and 41 have been amended to correct antecedent basis. Support for these amendments can be found throughout the specification, for example on page 5, lines 3-4. Claims 35 and 43 have been amended to recite "wherein said angiogenically active mutein has at least 75% sequence identity to the FGF-2 of SEQ ID NO:2 and retains at least 50% of the angiogenic activity of the FGF-2 of SEQ ID NO:2, and wherein said angiogenically active fragment has about 80% of the 146 residues of the FGF-2 of SEQ ID NO: 2 and retains at least 50% of the angiogenic activity of the FGF-2 of SEQ ID NO: 2." Support for this amendment can be found, for example, on page 16, line 25, continuing through page 17, line 5, where angiogenically active muteins are described, and on page 15, lines 19-22, where angiogenically active fragments are described. Claims 35 and 43 have also been amended to recite the claim limitation that "administration of said unit dose provides for coronary angiogenesis in said patient." Support for this claim limitation resides throughout the specification, for example, at page 5, lines 3-14. Claim 48 has been amended to recite "coronary vessels," to provide proper antecedent basis. No new matter has been added by way of claim amendment. Entry of these claim amendments into the above-identified application is respectfully requested.

Claims 35-52 remain pending in the application. The Examiner's remarks in the Office Action are addressed below in the order set forth therein.

The Rejections of the Claims Under 35 U.S.C. §103 Should Be Withdrawn

Claims 35, 36, 43, and 44 are rejected under 35 U.S.C. §103(a) as being unpatentable over Laham *et al.* (*J. Am. Coll. Cardiol.*, March 1998) in view of Deisher *et al.* (U.S. Patent No. 5,989,866). This rejection is respectfully traversed.

The presently claimed invention is directed to administration of a single unit dose of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof into one or more coronary vessels or into a peripheral vein of a human patient to treat a human patient suffering from congestive heart failure. Administration of the single unit dose of the recombinant FGF-2 or angiogenically active fragment or mutein thereof provides for coronary angiogenesis in said patient. The specification defines "coronary angiogenesis" as the formation of new blood vessels, ranging in size from capillaries to arterioles which act as collaterals in coronary circulation (at page 5, lines 12-14). Applicant respectfully submits that the cited references alone or in combination do not teach or suggest the methods of the present invention.

Laham *et al.* state that they have previously demonstrated that perivascular delivery of basic fibroblast growth factor (bFGF, FGF-2) results in functionally significant angiogenesis in an animal model of chronic myocardial ischemia. Laham *et al.* presently teach perivascular delivery of bFGF as being the implantation of bFGF-heparin alginate microcapsules in the epicardial fat surrounding a non-graftable vessel in the heart of human patients. As the Examiner states for the record, "Laham does not specifically teach the administration of bFGF via a coronary vessel or into a peripheral vein" (Office Action mailed May 7, 2003; hereinafter "the Office Action").

Applicant respectfully submits that the bFGF-heparin alginate microcapsules used by Laham *et al.* are slow-release drug delivery devices, providing local release of FGF-2 for an extended period of time. Furthermore, the patients receiving these bFGF-heparin alginate microcapsules also received coronary artery bypass grafting (CABG). From the disclosure provided in this reference, one cannot ascertain whether the increased perfusion in the ungraftable myocardial area was due to the CABG and/or due to the implantation of the bFGF-

heparin alginate microcapsules. This cited reference merely concludes that perivascular administration of these microcapsules was well tolerated in these recipients.

That being said, Applicant submits that the use of a slow-release drug delivery device such as that taught by Laham *et al.* is to be contrasted to the single unit dose of FGF recited in Applicant's claimed invention. Applicant has discovered that a single administration of the recited unit dose of FGF-2 or angiogenically active fragment or mutein thereof into a coronary vessel or peripheral vein surprisingly provides for coronary angiogenesis in the absence of a sustained-release delivery device or multiple administrations of this therapeutic agent. Such a beneficial result would not have been predicted based on the teachings of Laham *et al.* Rather, the fact that Laham *et al.* teach prolonged exposure to bFGF actually teaches away from Applicant's claimed invention.

As the Examiner has made of record, the Laham *et al.* reference fails to teach administration of FGF-2 or angiogenically active fragment or mutein thereof into a coronary vessel or into a peripheral vein. The Examiner relies on the combination of the teachings of the Laham *et al.* reference with the teachings of the Deisher *et al.* reference to support this obviousness rejection. However, Applicant contends that the motivation to combine these reference teachings is lacking in view of the distant relationship between the two FGF family members disclosed therein. Furthermore, even if one of skill in the art were motivated to combine the teachings of these two references, there would be no reasonable expectation of successfully modifying these two references to arrive at Applicant's claimed invention.

Deisher *et al.* teaches novel polynucleotides and polypeptide molecules of zFGF-5, which the patentees have assigned to the FGF family based on sequence homology. While Deisher *et al.* states that zFGF-5 may be used in treatment of disorders associated with congestive heart failure and other indications where angiogenesis is of benefit, one of skill in the art would not interpret the data presented therein as being predictive of the use of the zFGF-5 molecule for treatment of congestive heart failure, nor would they readily attribute angiogenic activity to the zFGF-5 molecule based on the mitogenic data presented in the Deisher *et al.* patent.

The Examiner states that Deisher *et al.* "demonstrates that zFGF-5 has the *in vivo* activity of inducing cardiac mitogenesis" and points to Examples 4 and 5 of the Deisher *et al.* patent in support of this statement. However, Applicant again makes of record the fact that Example 4 of the Deisher *et al.* patent demonstrates *ex vivo* mitogenic activity of a zFGF-5-Hep2 fusion on left and right ventricles isolated from mice (Example 4). Example 5 of this cited patent prophetically measures the effect of intraperiocardially injected zFGF-5 on cardiac regeneration in neonatal and adult rats by determining heart weight and function. Thus, neither of these two examples demonstrates *in vivo* cardiac mitogenesis activity of zFGF-5, nor do they demonstrate or suggest that zFGF-5 when administered into one or more coronary vessels or into a peripheral vein would provide *in vivo* angiogenic activity.

Applicant again notes that Deisher *et al.* provide no evidence that zFGF-5 or its muteins have angiogenic activity or mitogenic activity for endothelial cells, which activities would contribute to coronary angiogenesis. Coronary angiogenesis is a necessary requisite of Applicant's claimed invention. In addition to Examples 4 and 5 described above, the examples set forth in the Deisher *et al.* patent measure the *in vivo* mitogenic activity of adenovirus-produced zFGF-5 on cultured murine myocytes inoculated with an adenoviral-zFGF-5 construct (Example 3B), *in vivo* mitogenic activity of a zFGF-5-MBP (maltose binding protein) fusion on cultured murine myocytes (Example 3C), and *in vivo* mitogenic activity of adenovirus-produced zFGF-5 on murine osteoblasts (Example 7B), and reportedly demonstrate an increase in murine heart size when an adenoviral-zFGF construct comprising zFGF-5 is administered IV to mice (Example 8). None of these examples were designed to measure angiogenic activity of the zFGF-5 molecule or its mitogenic activity on endothelial cells.

Applicant again respectfully submits that such evidence of mitogenic activity on cultured murine myocytes and murine osteoblasts would hardly be interpreted by one of skill in the art as providing the basis for a reasonable expectation of success for the use of zFGF-5 to treat human patients with congestive heart failure. Nor does this evidence suggest to one of skill in the art that FGF-2, a remotely related member of the FGF family, should be administered *into one or more coronary vessels or into a peripheral vein* of a patient in need of treatment for congestive

heart failure in order to achieve coronary angiogenesis, and thus provide relief from the symptoms of this chronic medical condition.

The invention of Deisher *et al.* is focused on using zFGF-5 to stimulate the proliferation of myocytes, resulting in remodeling of the heart tissue and renewal of the heart's ability to function, and osteoblasts, enhancing osteoblast-mediated bone formation. Though this cited reference suggests that zFGF-5 would have angiogenic activity based on its homology to other members of the family of FGF molecules, it provides no credible evidence that zFGF-5, or any of the mutein zFGF-5 molecules described by Deisher *et al.*, has angiogenic activity or would be useful for treating congestive heart failure in a human.

Furthermore, Applicant contends that one of skill in the art would not readily have attributed the disclosure of Deisher *et al.* as being relevant to utility of an FGF protein that shares only 31% homology to zFGF-5. In fact, when defining the scope of their invention, Deisher *et al.* refer to polypeptides that are "substantially homologous" to the zFGF-5 polypeptides of the invention as being encompassed. "Substantially homologous" polypeptides are defined as "having 50%, preferably 60%, more preferably at least 80%, sequence identity to the sequences shown in SEQ ID NO:2" (see column 11, at lines 54-60).

Applicant again points out the differences between zFGF-5 and FGF-2, which are described in Deisher *et al.* First of all, zFGF-5 is disclosed as being most closely related to FGF-8. FGF molecules have been divided into two families based on their structural and functional differences. FGF-1 and FGF-2 have been separated out from FGF-8 and zFGF-5 based on these differences. Similarities such as having a common six-amino-acid motif, and having a heparin-binding domain, do not indicate that the molecules are related enough to presume they will possess all of the same activities. Many growth factors are capable of binding to heparin, yet they do not all share the same activities. The fact that proteins may have structural or biochemical similarities does not provide a reasonable expectation of success that they would provide a similar therapeutic benefit.

With respect to the Examiner's comment that "zFGF-5 can be considered a mutein or comprising a fragment thereof FGF-2" (Office Action at page 5, lines 5-7), Applicant notes that

claims 35 and 43 have been amended to require that the FGF-2 muteins used in the methods of the present invention have at least 75% sequence identity to the FGF-2 of SEQ ID NO:2, and that the FGF-2 fragments have about 80% of the 146 residues of the FGF-2 of SEQ ID NO:2. Therefore, zFGF-5, having only 31% homology to the FGF-2 of SEQ ID NO:2, cannot be considered as being a mutein or fragment of FGF-2 as defined by the limitation recited in these claims.

To establish a *prima facie* case of obviousness (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine the reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations. MPEP §2143. As FGF-2 and zFGF-5 are only 31% identical, there is no motivation to substitute the distantly related FGF-2 for zFGF-5 in the Deisher *et al.* reference, and combine the resulting disclosure with the disclosure of Laham *et al.* to arrive at Applicant's claimed invention. Furthermore, Deisher *et al.* fails to provide the requisite guidance as to how its disclosure, or the combination of the teachings of Deisher *et al.* and Laham *et al.*, should be modified to arrive at Applicant's claimed invention. Though Deisher *et al.* generically refer to formulation of the zFGF-5 proteins of that invention for "parenteral, particularly intravenous or subcutaneous" administration (at column 26, lines 36-38), this cited reference fails to specifically teach or suggest administration of zFGF-5, or FGF-2, into one or more coronary vessels or into a peripheral vein in the context of treating congestive heart failure. Thus, the combination of the teachings of Deisher *et al.* and Laham *et al.* fail to teach or suggest all of the limitations recited in Applicant's claimed invention.

The Examiner is reminded that the prior art itself must provide the skilled artisan the motivation to combine the reference teachings or to modify these teachings to arrive at Applicant's claimed invention. In the present case, the Examiner has merely used Applicant's claims as a guide and selected secondary references that mention various aspects of the claimed invention. This is an improper standard. "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re*

Fine, 837 F.2d 1071, 1075, 5 USPQ 2d 1596, 1600 (Fed. Cir. 1988). The law is clear that without motivation to combine the references, a rejection under 35 USC §103 fails.

In view of these amendments and remarks, Applicant respectfully submits that Laham *et al.* in view of Deisher *et al.* does not render obvious the presently claimed invention, and this rejection should be withdrawn.

Claims 37 and 45 are rejected under 35 U.S.C. §103 as being unpatentable over Laham *et al.* (*J. Am. Coll. Cardiol.* March 1998) and Deisher *et al.* (U.S. Patent No. 5,989,866), further in view of Fiddes *et al.* (U.S. Patent No. 5, 604,293). This rejection is respectfully traversed.

As noted above, Laham *et al.* teach an entirely different objective than that accomplished by Applicant's invention. Thus, Laham *et al.* teach the use of a slow-release drug delivery device to achieve prolonged exposure to bFGF within the perivascular region in the myocardium of human patients with ischemic heart disease. In contrast, Applicant's claimed invention is based on the discovery that a single administration of the recited unit dose of FGF-2 or angiogenically active mutein or fragment thereof into one or more coronary vessels or into a peripheral vein provides for coronary angiogenesis in patients in need of treatment for congestive heart failure. This is achieved in the absence of slow-release drug delivery devices and in the absence of multiple administrations. The Examiner relies upon the combination of the Laham *et al.* and Deisher *et al.* references to arrive at Applicant's protocol. However, for the reasons stated above, Applicant respectfully submits that one of skill in the art would not have been motivated to combine the teachings of these two references. Laham *et al.* and Deisher *et al.* are directed to distantly related molecules, and while Deisher *et al.* suggest that zFGF-5 may be beneficial in treatment of congestive heart failure and in instances where angiogenesis would be helpful, this cited reference provides no evidence whatsoever that zFGF-5 has angiogenic activity, much less evidence that a single administration of zFGF-5 into one or more coronary vessels or into a peripheral vein would provide therapeutic benefit to a patient with congestive heart failure. Accordingly, Applicant respectfully submits that the requisite motivation to combine the teachings of these two cited references is lacking. Furthermore, for the reasons

noted above, even if one of skill in the art were motivated to combine the teachings of these two cited references, the combined teachings fail to teach or suggest all of the limitations recited in Applicant's claimed invention. In fact, the Laham *et al.* reference teaches a protocol that provides for prolonged exposure to bFGF, which teaches away from the short-term exposure provided by Applicant's claimed invention.

The methods of the present invention administer as a single unit dose a therapeutically effective amount of a recombinant FGF-2 or angiogenically active fragment or mutein thereof into one or more coronary vessels or into a peripheral vein in order to treat a human patient for congestive heart failure. The single unit dose provides for coronary angiogenesis in the patient, thereby providing relief from the symptoms associated with this chronic medical condition. The beneficial effects provided by the recited modes of administering FGF-2 as taught by Applicant could not have been predicted based on the combination of the teachings of the Laham *et al.* and Deisher *et al.* references.

As the requisite motivation to combine the Laham *et al.* and Deisher *et al.* references is lacking, it is improper to further combine the teachings of these two references with the teachings of the Fiddes *et al.* reference as the basis for rendering the presently claimed invention obvious. However, even if one of skill in the art were motivated to combine the teachings of all three of these references, one would not have a reasonable expectation of successfully modifying their respective disclosures to arrive at Applicant's claimed invention.

Fiddes *et al.* disclose the synthesis and manipulation of acidic (FGF-1) and basic (FGF-2) fibroblast growth factors and suggest that these sequences are useful in effecting a number of responses, including accelerated healing of wounds, bone fractures, burn tissue, degenerated neurological tissue, damaged myocardial tissue, or other trauma. However, Fiddes *et al.* are silent with respect to administration of FGF-2 into coronary vessels or into a peripheral vein of a human patient in need of treatment for congestive heart failure.

The Examiner asserts that Fiddes *et al.* state that the fibroblast growth factors are useful in effecting "damaged myocardial tissue." However, Fiddes *et al.* also state that the fibroblast growth factors are useful in treating "other trauma" (see column 3). These are very broad

statements regarding the utility of these growth factors. The only evidence provided in support of these statements pertains to the role of FGF in promoting wound healing. Example 12 demonstrates that subcutaneous implantation of polyvinyl alcohol sponges with bFGF in rats led to a higher amount of granulation than those without bFGF. This disclosure would not provide the requisite motivation to combine the teachings of Fiddes *et al.* with the teachings of both Laham *et al.* and Deisher *et al.* to arrive at Applicant's claimed invention.

The Examiner imprecisely states that "congestive heart failure is caused by conditions such as myocardial infarction, stroke, and heart attack" (see page 7 of the Office Action). Applicant respectfully notes that congestive heart failure represents a condition in which the heart muscle is damaged or overworked, and thus can't pump enough blood to the body's other organs. As blood flow out of the heart slows, blood returning to the heart through the veins backs up, causing congestion in the tissues. Congestive heart failure has many causes, only one of which may be myocardial infarction (or heart attack); myocardial infarction does not necessarily lead to congestive heart failure. Causes of congestive heart failure may include coronary artery disease, hypertension, abnormal heart valves, congenital heart disease, severe lung disease, and diabetes. Less common causes may include severe anemia, hyperthyroidism and arrhythmia or dysrhythmia. Stroke is not a cause of congestive heart failure; rather, congestive heart failure is one of many medical conditions that can lead to stroke.

Applicant respectfully submits that the requisite motivation to combine the teachings of Fiddes *et al.* with the teachings of both Laham *et al.* and Deisher *et al.* is lacking. The Examiner states that Fiddes *et al.* teach wound healing by subcutaneous implantation of FGF-2. Wound healing is a complex process that is distinct from congestive heart failure, and therefore the disclosure of Fiddes *et al.* would not motivate one of skill in the art to apply the teachings of Fiddes *et al.* to the treatment of congestive heart failure. The Examiner states that Fiddes *et al.* teach that angiogenic stimuli, provided by FGF, result in the release of tissue plasminogen and collagenase, and that the FGF proteins of the invention are also useful in the treatment of conditions such as stroke and heart attack. Fiddes *et al.* teach that the FGF proteins of the invention are useful in treatment of conditions that respond to tPA and collagenase, and list the

presence of a blood clot as an example of an indication that would enable a response to these enzymes. However, congestive heart failure would not necessarily be considered a condition that responds to collagenase or tPA (see the list of causes for congestive heart failure mentioned above). Furthermore, the Fiddes *et al.* reference only suggests intravenous administration of FGF-2 in the context of a method for maintaining a suitable level of tPA in the blood stream at the systemic level. This mode of administration is not taught or suggested in the context of treating congestive heart failure, nor does this reference provide the guidance to one of skill in the art to modify the teachings of the Laham *et al.* and Deisher *et al.* references to arrive at the two modes of administration recited as a limitation in Applicant's claimed invention.

The Examiner's reliance on the disclosure by Deisher *et al.* that FGF-2 has been shown to play a role in avian cardiac development and that FGF-2 and zFGF-5 have both been shown to induce coronary collateral development in animal models is noted. However, Applicant contends that this does not provide the requisite motivation to combine the teachings of Deisher *et al.* with the teachings of Fiddes *et al.* and Laham *et al.* to arrive at Applicant's claimed invention. First of all, processes involved in organ and tissue development (especially in an avian model) would not necessarily be relevant for the treatment of congestive heart failure in human patients. Secondly, the canine animal model has been noted as being particularly inappropriate for comparison to humans, due to the abundance of naturally occurring collateral circulation. Though the utility of animal models is not being disparaged, Applicant contends that these particular statements by Deisher *et al.* do not provide any motivation to combine the teachings of Deisher *et al.* with those of Laham *et al.* or Fiddes *et al.* to arrive at the presently claimed invention.

The Examiner states that "one skilled in the art would be motivated to use FGF-2 to treat congestive heart failure because the literature does not teach against it." This statement is misleading, and incorrect. To establish a *prima facie* case of obviousness (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine the reference

teachings. The absence of any literature teaching away from the combination does not, in itself, provide the requisite motivation.

For all of these reasons, Applicant respectfully submits that one of skill in the art would not be motivated to combine the references of Laham *et al.*, Deisher *et al.*, and Fiddes *et al.* to arrive at the presently claimed invention. Accordingly, this rejection should be withdrawn.

Claims 38-41, 42, and 47-49 are rejected under 35 U.S.C. §103 as being unpatentable over Laham *et al.* (*J. Am. Coll. Cardiol.*, March 1998) in view of Deisher *et al.* (U.S. Patent No. 5,989,866), Fiddes *et al.* (U.S. Patent No. 5, 604,293), Wilson *et al.* (U.S. Patent No. 5,612,211), and Unger *et al.* (U.S. Patent No. 5,244,460). This rejection is respectfully traversed.

The teachings of the Laham *et al.*, Deisher *et al.*, and Fiddes *et al.* references are described above. Applicant respectfully submits that, for the reasons noted above, the requisite motivation to combine these three references is lacking, and thus the combination of these three references with the teachings of Wilson *et al.* and Unger *et al.* is improper. However, even if one of skill in the art were motivated to combine the teachings of all five of these references, Applicant respectfully submits that the requisite guidance as to how to modify these five references to arrive at Applicant's claimed invention is lacking.

As the Examiner notes, the Laham *et al.*, Deisher *et al.*, and Fiddes *et al.* references do not teach the claim limitation of administering heparin, particularly in combination with administration of FGF-2 into one or more coronary vessels or into a peripheral vein of a human patient to treat congestive heart failure. Applicant submits that the teachings of Wilson *et al.* and Unger *et al.* combined with the teachings of Laham *et al.*, Deisher *et al.*, and Fiddes *et al.* do not teach or suggest all of the limitations of Applicant's claimed invention.

As previously made of record, Wilson *et al.* teach the use of FGFs for the stimulation of growth, differentiation, or culture of stem cells, for subsequent use in diagnostic, therapeutic, and research applications. This cited reference also teaches the use of heparin to potentiate the stimulatory effect of "concentrations of an FGF *administered to a hematopoietic cell donor, recipient or subject according to a method of the present invention*" (at column 12, lines 52-55;

emphasis added). The invention of Wilson *et al.* is directed to FGF stimulation of stem cells, for purposes of treating a long list of diseases or pathologies, including various degenerative diseases, where an increased number of stem cells would be beneficial. *No mention is made of congestive heart failure, or any other cardiac disease.* Therefore, there is no motivation to combine the reference of Wilson *et al.* with any of the other references cited.

Furthermore, Wilson *et al.* discloses the use of heparin to influence hematopoiesis, which is not a goal of the methods of the present invention. The present invention uses heparin to reduce FGF-2 clearance, as is clearly stated throughout the specification; see, for example, Figure 3, and page 40, lines 13-20.

The facts cited by the Examiner that FGFs increase proliferation, stimulation, growth, and/or differentiation of blood cells, that heparan sulfate is known to be a component of the extracellular matrix that influences hematopoiesis, that growth factors bind heparin, that hematopoiesis is the formation and development of blood cells, and that members of the FGF family are characterized by heparin-binding domains, do not render obvious the use of heparin with FGF-2 to treat a patient with congestive heart failure, whereby the therapeutic benefit of coronary angiogenesis is provided. Furthermore, the statement made by the Examiner that neovascularization requires hematopoiesis is not supported by any of the references cited by the Examiner. Applicant asks that the Examiner provide evidence supporting this statement. There is no obvious relationship between hematopoiesis and the use of heparin with FGF-2 to treat congestive heart failure, and therefore, the disclosure of Wilson *et al.* is irrelevant to the methods of the presently claimed invention.

With respect to the statement in Wilson *et al.* that FGF "has been used for the treatment of ischemic heart disease" where it was found to increase blood flow in the heart for sustained periods of time after myocardial infarction (U.S. Patent Nos. 4,296,100 and 4,378,347 to Franco), Applicant again emphasizes that the work of Franco was based on animal models of acute myocardial infarction, where FGF was administered by myocardial injection. The presently claimed invention is directed to treatment of *congestive heart failure* by administration of *a single unit dose* of recombinant FGF-2 or angiogenically active fragment or mutein thereof

into one or more coronary vessels or into a peripheral vein. The Examiner reasons that Applicant has not defined congestive heart failure as a chronic ischemic event, and therefore no weight can be accorded to the statement that congestive heart failure is a chronic, versus an acute, ischemic event. However, Applicant respectfully submits that one of skill in the art would readily interpret "congestive heart failure" as being a chronic ischemic condition based on the well-accepted clinical definition for this condition. See, for example, "Heart and Stroke Facts," at pages 61-62, available on-line from the American Heart Association, which pages are submitted concurrently herewith as Appendix A. In view of the distinction between myocardial infarction and congestive heart failure, and in view of the differing modes of administration taught by Franco and recited in the presently claimed invention, Applicant maintains that one would not construe the work of Franco as providing any reasonable expectation of successfully using FGF to treat congestive heart failure in the manner set forth in Applicant's claimed invention. Furthermore, the fact that Wilson *et al.* reference Arakawa *et al.* as stating that bFGF appears to induce neovascularization, re-epithelialization, and wound repair would also not motivate someone to use this molecule in treating congestive heart failure, for the same reasons. There is no reasonable expectation of success in treating a complex disease like congestive heart failure based on such limited and indefinite information. This fact is true even if the entirety of the disclosure of Wilson *et al.* is combined with the teachings of Laham *et al.*, Deisher *et al*, and Fiddes *et al.*

Unger *et al.* teach a method for treating atherosclerosis by injecting FGF-2 via a catheter into a coronary artery. As Applicant has previously made of record, the invention disclosed in this cited reference requires repeated injections until improved cardiac blood flow has been obtained. In contrast, the current invention provides a method for treating a human patient for congestive heart failure, comprising administering a single unit dose of a therapeutically effective amount of an FGF-2 or angiogenically active fragment or mutein thereof into one or more coronary vessels or into a peripheral vein in a human patient. Administering a single unit dose of FGF-2 in accordance with the methods of the present invention provides for coronary angiogenesis that translates into a prolonged therapeutic benefit for a subject with congestive

heart failure. Such a protocol is not contemplated or even suggested by Unger *et al.* In fact, this cited reference teaches away from administration of a single unit dose of FGF-2 for congestive heart failure. See the specification at column 2, line 32, continuing through column 3, line 10, where Unger *et al.* summarize the drawbacks of the teachings of Franco, U.S. Patent No. 4,296,100, and the need for repeated injections of FGF-2 to achieve growth of blood vessels in the heart of a patient. Thus, Applicant's claimed method has achieved surprising results that would not have been predicted by the cited prior art, particularly Unger *et al.* and Laham *et al.*, which disclose protocols that teach away from Applicant's claimed invention. Furthermore, Unger *et al.* do not teach administration into a peripheral vein, but limit the administration of FGF-2 to inserting a catheter into a coronary artery and providing an infusion port through which the FGF-2 composition is *repeatedly* injected. Thus Unger *et al.* fail to teach those claim limitations not taught or suggested by Laham *et al.*, Deisher *et al.*, *Fiddes et al.*, and Wilson *et al.*

Applicant respectfully submits that there is no motivation to combine the disclosure of Wilson *et al.* with any of the other cited references. Furthermore, Unger *et al.* teach away from Applicant's claimed invention. Even if one of skill in the art were motivated to combine the teachings of all five of these cited references, the combined disclosures do not teach all the limitations of the instant claims, and the rejection should be withdrawn.

In summary, one of skill in the art would not have been motivated to modify any of these cited references, or to combine the teachings of these cited references, to arrive at Applicant's invention, nor would a reasonable expectation of success have been supported by the teachings of any of these cited references. Further, these cited references alone or in combination do not teach or suggest all of the limitations recited in the pending claims. For all of these reasons, Applicant respectfully submits that a *prima facie* case of obviousness has not been established, and all of these rejections under 35 U.S.C. §103 should be withdrawn.

The Rejection of the Claims Under the Judicially Created Doctrine of Obviousness-Type Double Patenting Should Be Withdrawn

Claims 25-52 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-58 of U.S. Patent No. 6,440,934 B1 (the '934 patent). This rejection is respectfully traversed.

The instant claims are drawn to a method for treating a human patient for congestive heart failure, comprising administering a single unit dose of a therapeutically effective amount of a recombinant FGF-2 or an angiogenically active fragment or an angiogenically active mutein thereof into one or more coronary vessels or into a peripheral vein in a human patient in need of treatment for said congestive heart failure, where the therapeutically effective amount is about 0.2 μg/kg to 48 μg/kg of patient weight. The instant claims are also drawn to a method for treating a human patient for congestive heart failure, comprising administering a single unit dose of a recombinant FGF-2 or an angiogenically active fragment or an angiogenically active mutein thereof into one or more coronary vessels or into a peripheral vein in a human patient in need of treatment for congestive heart failure, where the unit dose comprises from about .008 mg to 7.2 mg of the recombinant FGF-2 or angiogenically active fragment or angiogenically active mutein thereof. In both methods, the angiogenically active mutein has at least 75% sequence identity to the FGF-2 of SEQ ID NO:2 and retains at least 50% of the angiogenic activity of the FGF-2 of SEQ ID NO:2, and the angiogenically active fragment has about 80% of the 146 residues of the FGF-2 of SEQ ID NO: 2 and retains at least 50% of the angiogenic activity of the FGF-2 of SEQ ID NO: 2. Administration of the single unit dose of recombinant FGF-2 or angiogenically active fragment or mutein thereof provides for coronary angiogenesis, which translates into a prolonged therapeutic benefit for patients with congestive heart failure.

The claims of the '934 patent are drawn to a method for treating a human patient for coronary artery disease, a method for inducing angiogenesis, a method for treating a human patient for a myocardial infection, and a method for providing a human patient with relief from symptoms of angina. The Examiner states that congestive heart failure is a genus that encompasses the species of diseases reflected in the '934 patent (coronary artery disease and

myocardial infarction), and that congestive heart failure would include angina and that administration of FGF-2 would cause angiogenesis. Applicant respectfully disagrees.

Applicant respectfully submits that there is no genus/species relationship between congestive heart failure and the diseases disclosed in the '934 patent. First of all, as mentioned above, congestive heart failure has many causes, including coronary artery disease, myocardial infarction, hypertension, abnormal heart valves, heart muscle disease or inflammation, congenital heart disease, severe lung disease, diabetes, severe anemia, hyperthyroidism, or abnormal heart rhythm. Therefore, a patient may have congestive heart failure in the absence of myocardial infarction or coronary artery disease. Similarly, a patient may have coronary artery disease or myocardial infarction without having congestive heart failure. Therefore, congestive heart failure is not a genus that encompasses diseases such as myocardial infarction and coronary artery disease.

Furthermore, while edema and shortness of breath frequently accompany congestive heart failure, angina is not necessarily a symptom of this medical condition. Therefore, the statement by the Examiner that "chest pain would occur in congestive heart failure" is not accurate.

Finally, although the claims of the '934 patent recite a method for inducing angiogenesis in the heart of a human patient, the method requires administration into coronary vessels or peripheral veins of a patient in need of treatment for coronary artery disease. In contrast, the instant claims are drawn to methods for treating congestive heart failure, which, for reasons noted above, can occur in the absence of coronary artery disease. The claims of the '934 patent, and the supporting disclosure within the '934 specification, do not teach or suggest the methods of treating congestive heart failure that are recited in the instant claims.

Therefore, claims 1-58 of the '934 patent do not render obvious the instant invention. Accordingly, this rejection of the claims should be withdrawn.

CONCLUSION

In view of the above amendments and remarks, Applicant submits that the rejections of the claims under 35 U.S.C. §103 and the obviousness-type double patenting rejection are overcome. Applicant respectfully submits that this application is now in condition for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

Leslie T. Henry

Leslie T. Henry
Registration No. 45,714

Customer No. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the US Patent and Trademark Office at facsimile number (703) 872-9306 on the date shown below.

Lynda Jo Pixley

Lynda Jo Pixley

9/8/03
Date

APPENDIX A

Table of Contents

Congestive Heart Failure

What is congestive heart failure?

Congestive heart failure (or heart failure) is a condition in which the heart can't pump enough blood to the body's other organs. It occurs because the heart muscle is damaged or overworked. This can result from

- narrowed arteries that supply blood to the heart muscle — coronary artery disease.
- past heart attack (myocardial infarction) with scar tissue that interferes with the heart muscle's normal work.
- high blood pressure.
- heart valve disease due to past rheumatic fever or other causes.
- primary disease of the heart muscle itself, called cardiomyopathy.
- heart or blood vessel defects present at birth — congenital heart disease.
- infection of the heart valves (endocarditis) and/or heart muscle itself (myocarditis).

The "failing" heart keeps working but not as well as it should. People with heart failure can't exert themselves, because they become short of breath and tired.

As blood flow out of the heart slows, blood returning to the heart through the veins backs up, causing congestion in the tissues. Often swelling (edema) results. Most often the legs and ankles swell, but other parts of the body can swell, too. Sometimes fluid collects in the lungs and interferes with breathing, causing shortness of breath, especially when a person is lying down.

Heart failure also affects the kidneys' ability to dispose of sodium and water. The retained water increases the edema.

How is congestive heart failure diagnosed and treated?

The most common signs of congestive heart failure are swollen legs or ankles or difficulty breathing. Another symptom is weight gain when fluid builds up.

> Congestive heart failure usually requires a treatment program of rest, proper diet, modified daily activities and prescribed drugs.

Various drugs are used to treat congestive heart failure. They perform different functions. **ACE (angiotensin converting enzyme) inhibitors** and **vasodilators** expand blood vessels and decrease resistance. This lets blood flow more easily and makes the heart's work easier or more efficient. **Beta blockers** can improve how well the heart's left lower chamber (left ventricle) works. **Digitalis** strengthens the heart's pumping action. **Diuretics** help the body eliminate excess salt and water.

When a specific cause of congestive heart failure is discovered, it should be treated or, if possible, corrected. For example, some cases of congestive heart failure can be treated by treating high blood pressure. If the congestive heart failure is caused by an abnormal heart valve, the valve can be surgically replaced.

Most cases of mild and moderate congestive heart failure are treatable. Proper medical supervision can prevent such people from becoming invalids.

If the heart becomes so damaged that it can't be repaired, a more drastic approach should be considered. A heart transplant could be an option.

What about heart transplants?

A heart may be irreversibly damaged by long-lasting heart disease or viral infection. People with long-term heart failure, heart muscle disease, or other irreversible heart injury from coronary artery disease and multiple heart attacks that can't be treated by any other medical or surgical means may be candidates for heart transplants.

When the heart can no longer adequately work and a person is at risk of dying, a heart transplant may be indicated. It involves removing a diseased heart and replacing it with a healthy human heart. Cardiac transplantation is recognized as a proven procedure in appropriately selected patients.

When do infants and children need heart transplants?

Children with complex forms of congenital heart defects and children with dilated cardiomyopathy (see page 63) are most likely to be potential recipients.

Hypoplastic left heart syndrome is the most common, complex congenital heart defect for which a heart transplant is a potentially useful treatment. In this condition the heart's lower left pumping chamber (left ventricle) and the large artery that carries blood to the body (ascending aorta) are too small to support normal blood flow.

Other Heart and Blood Vessel Diseases

What is bacterial endocarditis?

Bacterial endocarditis is an infection of the heart's inner lining (endocardium) or the heart valves. This can damage or even destroy the heart valves. It occurs when bacteria in the bloodstream (bacteremia) lodge on abnormal heart valves or other damaged heart tissue.

Certain bacteria normally live on parts of your body, such as the mouth and upper respiratory system, the intestinal and urinary tracts, and the skin. Some surgical and dental procedures cause a brief bacteremia. Bacteremia is common after many invasive procedures, but only certain bacteria commonly cause endocarditis.

Endocarditis rarely occurs in people with normal hearts. People who have these preexisting heart conditions are at risk for developing endo-carditis when a bacteremia occurs:

- artificial (prosthetic) heart valves
- a history of previous endocarditis
- heart valves damaged (scarred) by rheumatic or other heart disease
- congenital heart or heart valve defects
- hypertrophic cardiomyopathy (See page 64.)

People who've had endocarditis before are at risk of getting it again, even when they don't have heart disease. Some congenital heart defects, including a ventricular septal defect, an atrial septal defect, or a patent ductus arteriosus, can be successfully repaired surgically. (See pages 54, 55 and 57.) There's no longer an increased risk for endocarditis after that.